II. RESPONSE TO OFFICE ACTION

A. Status of Claims

In response to a Restriction Requirement dated June 17, 2004, Applicants elected to pursue the Group I claims, which encompassed claims 1-100. Applicants further elected epirubicin as a species. Consequently, claims 19-40, 42, 44-65, 67, 72-93, and 101-108 were withdrawn from consideration. In the Office Action Dated September 28, 2004 ("Action"), claims 1-18, 41, 43, 66, 68-71, and 94-100 were rejected.

In this response, claims 3 and 4 have been cancelled and claims 1, 2, 43, 68, and 99-100 have been amended. Support for the amendments can be found throughout the specification, for example, at page 4, lines 4-7; page 6, line 23 to page 7, line 27, and in the originally filed claims. Consequently, the amendments do not introduce matter for which a new search is required.

Thus, claims 1, 2, and 5-100 are the subject of this response.

B. Claim Objections

Claim 1 has been amended in a non-limiting manner to correct a typographical error. The word "UGTB7" has been amended to recite "UGT2B7."

C. Claims Are Enabled

The Action rejects claims 1-18, 41, 43, 66, 68-71, 94-100 under 35 U.S.C. § 112, first paragraph, because the specification allegedly does not reasonably provide enablement for all methods for determining a dose of any UGT2B7-glucuronidated drug by assaying for the level of UGT2B7 activity, assaying for the activity of UGT2B7 or assaying for the presence of any polymorphism in the UGT2B7 gene or other unstated gene as a means for determining the dose of any UGT2B7-glucuronidated drug. More specifically, it contends that the specification has not established a correlation between glucuronidation of epirubicin and any particular polymorphism in the UGT2B7 gene or changes in the level or activity of UGT2B7. It argues that even though the specification is enabling for methods involving morphine based on polymorphisms at -161 or +801/+802 in the UGT2B7 gene, these results cannot be extrapolated to other UGT2B7-glucuronidated drugs because the activity of UGT2B7 variants differs with respect to the drug and with respect to the particular UGT2B7 variant. Applicants respectfully traverse this rejection.

The methods deemed enabling with respect to morphine can be extrapolated to epirubicin because the inventors provide evidence in the specification that there is a correlation between glucuronidation of morphine and glucuronidation of epirubicin. Under Example 7, which is entitled "Correlation study," it states"

> Since morphine is glucuronidated by UGT2B7 (Coffman et al., 1997), correlation between epirubicin and morphine glucuronidation rates was assessed in 47 normal human liver microsomes. Formation of epirubicin glucuronide was significantly related to that of M3G ($r=0.76$, $p<0.001$) and M6G ($r=0.73$, $p<0.001$) (FIG. 4A and 4B, respectively).

Page 104. The specification teaches that the conversion of morphine to either M3G or M6G is correlated with the genotype at position -160 (page 109). Therefore, it would not require undue experimentation to practice the invention with respect to epirubicin because of the correlation data.

Furthermore, it would not require undue experimentation to practice the claimed invention to the extent it recites "a UGT2B7-glucuronidated drug" because the skilled artisan is taught by the current specification that two different drugs—morphine and epirubicin—are glucuronidated differently depending on the genotype at position -160 in the *UGT2B7* gene. The skilled artisan is also taught that correlation evidence can be gathered (page 104 and FIG. 4A-C) and others ways in which the glucuronidation of UGT2B7 substrates can be evaluated based on the morphine date. Therefore, it would not require any undue experimentation to practice the full scope of the invention.

The Action cites several articles in support of the position that there was a high level of unpredictability with respect to UGT2B7 polymorphisms. The articles of Bhasker, Innocenti and Toide, however, do not specifically discuss or address the polymorphism at position -160 of the *UGT2B7* gene. The invention currently claimed is directed to "determining the nucleotide sequence at position -161 in one *UGT2B7* gene," and therefore, the cited references do not indicate that the claimed invention would not work with respect to epirubicin.

Applicants further note that the Toide reference is not relevant in the context of the present invention. The Action contends that Toide "supports the finding that it is unpredictable whether UGT2B7 mRNA levels are associated with changes in enzyme activity." This article is not relevant because the data presented and currently relied upon is based on enzyme activity and

the correlation between different glucuronidated drugs, and not mRNA levels. Though mRNA levels may or may not ultimately be involved in the correlation between the polymorphism at -160 and activity, this is not appear to be relevant to the current argument.

D. Claims Are Definite

The Action rejects claims 10, 43, 66, 68-71 and 94-100 under 35 U.S.C. § 112, second paragraph, as indefinite . Applicants respectfully traverse these rejections.

1. Claim 10

The rejection of claim 10 is rendered moot as claim 10 was canceled for being dependent on another claim that was canceled.

2. Claims 43 and 66

Claims 43 and 66 were rejected as indefinite for the recitation of "determining the activity of UGT2B7 in a patient according to the method." Claim 43 has been amended so that it recites "determining the activity of UGT2B7 in a patient according to the method of claim 1." Claim 66, nor any other claim (except claim 43), appears to have this limitation.

The Action also points out some redundancy in claim 43. The term "to administer" has been deleted.

3. Claims 68-71

The Action rejects claims 68-71 because the claims are drawn to methods for evaluating the risk of toxicity from a UGT2B7-glucuronidated drug, but it contends the claims do not clarify how the step of determining a nucleotide sequence results in the evaluation of the risk of toxicity. Applicants respectfully traverse this rejection.

The claims have been clarified to indicate that determining the nucleotide sequence at position -161 is to determine the level of UTG2B7 activity or expression, which was already clear from originally filed claims 1 and 2, and therefore, this does constitute a limiting amendment because the limitation of dependent claim 2 was already recited by claims 68-71. Moreover, on page 2 of the specification, it indicates that the "main detoxifying pathway for epirubicin is the formation of epirubicin glucuronide. . . ." It later indicates on page 3 that epirubicin glucuronide is inactive, water soluble and readily excreted in the bile and urine.

UGT2B7 mediates the glucuronidation of UGT2B7-glucuronidated drugs. Furthermore, the specification states:

> The level of glucuronidation activity of UGT2B7 with respect to a UGT2B7 substrate can be predicted depending upon the sequence of base -161 in the promoter for the gene encoding UGT2B7. As discussed herein, patients with thymidine residues at position -161 in both UGT2B7 promoters will be considered to have the highest level of UGT2B7 activity ("high glucuronidators"); patients with one thymidine residue and one cytosine residue at position -161 in each UGT2B7 promoter have the next highest level of UGT2B7 activity ("intermediate glucuronidators"); and, patients with cytosine residues at position -161 in both UGT2B7 promoters have the lowest level of UGT2B7 activity ("low glucuronidators"). Therefore, persons with a T/T genotype at position -161 are considered to have a high level of UGT2B7 activity, persons with a C/T genotype at that position are considered to have an intermediate level of UGT2B7 activity, and persons with a C/C genotype at position -161 are considered to have a low level activity (when a base from only one promoter is known, it will be known that the person is an intermediate or high glucuronidator if that one nucleotide is a T, while a person with one identified base at -161 that is a C is an intermediate or low glucuronidator). Page 13.

As a result, the glucuronidation activity of UGT2B7 is indicative of how much glucuronidation there will be of a UGT2B7-glucuronidated drug, *i.e.,* how much of the active, toxic version of the drug there is compared to how much of the inactive, nontoxic version of the drug there is. Therefore, it is clear that the claims are directed to a method for evaluating the risk of toxicity from a UGT2B7-glucuronidated drug. Applicants respectfully request the rejection be withdrawn.

4. Claims 94-98

The Action rejects claims 94-98 as indefinite because it contends the claims are drawn to methods for screening an individual for glucuronidation activity yet they recite a final step of identifying the nucleotide sequence of a polymorphism. Applicants respectfully traverse this rejection.

As discussed above regarding rejected claims 68-71, the specification teaches there is a correlation between nucleotide sequence and the level of UGT2B7 activity or expression. UGT2B7 mediates glucuronidation. Therefore, identifying a nucleotide sequence of a polymorphism that correlates with glucuronidation activity in the individual is a way of

screening an individual for glucuronidation activity. Accordingly, the claim is definite and the rejection should be withdrawn.

5. Claim 99

The Action rejects claim 99 as indefinite because it contends the claim is drawn to a method for prescribing a dose of a UGT2B7-glucuronidated drug, yet the final step is one for determining the level of UGT2B7 activity. Applicants respectfully traverse this rejection.

The skilled artisan is aware that the amount of a drug that is prescribed to a patient may involve considering toxicity issues with respect to that patient. The present specification says at much: "According to methods provided by the invention, these results will be used to adjust and/or alter the dose of epirubicin or other agent administered to an individual in order to reduce drug side effects." Specification at page 63. As discussed with respect to the rejection of claims 68-71, determining the level of UGT2B7 activity has ramifications with respect to the risk of toxicity. Consequently, the skilled artisan would understand that determining the level of UGT2B7 activity could impact the prescribing of a UGT2B7-glucuronidated drug in the patient whose level of UGT2B7 activity was assessed. Accordingly, the claim is not indefinite.

6. Claim 100

The Action rejects claim 100 as indefinite because it contends the claim is drawn to a method for predicting the degree of an epirubicin-induced toxicity, yet the final step is one for determining the nucleotide sequence at position -161. Applicants respectfully traverse this rejection.

The claim has been clarified to indicate that determining the nucleotide sequence at position -161 is to determine the level of UTG2B7 activity or expression, which was already clear from originally filed claims 1 and 2, and therefore, it does not constitute a limiting amendment because the limitation of dependent claim 2 was already recited by claim 100.

As discussed above, the specification indicates that the "main detoxifying pathway for epirubicin is the formation of epirubicin glucuronide. . . ." It later indicates on page 3 that epirubicin glucuronide is inactive, water soluble and readily excreted in the bile and urine. UGT2B7 mediates the glucuronidation of UGT2B7-glucuronidated drugs. Therefore, it is clear

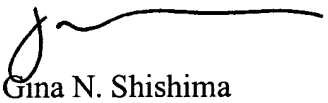
that the claim is directed to a method for predicting the degree of epirubicin-induced toxicity. Applicants respectfully request the rejection be withdrawn.

CONCLUSION

Applicants believe that the foregoing remarks fully respond to all outstanding matters for this application. Applicants respectfully request that the rejections of all claims be withdrawn so they may pass to issuance.

Should the Examiner desire to sustain any of the rejections discussed in relation to this Response, the courtesy of a telephonic conference between the Examiner, the Examiner's supervisor, and the undersigned attorney at 512-536-3081 is respectfully requested.

Respectfully submitted,



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Date: March 28, 2005